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Synthesis, Identification and Evaluation of Antimicrobial Activity of some New N-Substituted-2-(methylthio) benzimidazole Containing Heterocyclic Ring

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ABSTRACT

New derivatives of 1,2,3-triazole and pyrazole were obtained from the work that was conducted in this research. Firstly, reaction of 2-Mercaptobenzimidazole (2-MBI) in a basic condition with methyl iodide gave 2-(methylthio)-1H-benzo[d]imidazole then compound (1) was reacted with sodium hydride in Dimethylformamide (DMF) at (0°C) to bring forth the salt of compound (1); subsequently, the produced salt was reacted with chloroacetylchloride to produce 2-chloro-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone as starting compound (2). Thereafter, reaction of compound (2) was carried out through two pathways: first pathway, involved a reaction with sodium azide to give 2-azido-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone compound (3) which was entered in 1,3-dipolar cycloaddition with α,β-unsaturated carbonyl compounds (a-e) to give 1,2,3-triazole derivatives (4a-e). While the second pathway was achieved by reaction with p-phenylenediaimine to give compound (5) then diazoniation to produce diazonium salt which was, in turn, coupled with acetylacetone to give compound (6). Subsequently, the product of the previous reaction was reacted with hydrazine derivatives (a-e) to give pyrazole derivatives (7a-e). The new prepared compounds were identified by Fourier Transform Infrared (FTIR), Proton Nuclear Magnetic Resonance (^{1}H-NMR) and Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR) and their physical properties were measured. Furthermore, we have evaluated the effect of some prepared compounds on some bacterial and fungal strains.

Keywords: 2-mercaptobenzimidazole, 2-(methylthio)benzimidazole, 1,2,3-triazole, Pyrazole, Antimicrobial

INTRODUCTION

Heterocyclic compounds constitute a key-component in numerous natural products, to name a few; vitamins, hormones, alkaloids, a wide range of antibiotics, pharmaceutical products, herbicides, anti-aging medicines and plenty other industrial products of high importance (different types of dyes, corrosion inhibitors, stabilizing agents, sensitizers, etc.,) [1]. In fact, more than half of all known organic compounds are heterocycles [2]. So far, 2-mercaptobenzimidazoles are the most frequently encountered heterocyclic in medicinal and industrial chemistry [3], with a wide variety of essential biological activities such as antihistamine, antimicrobial, neutropic and analgesic activities [4]. 2-Mercaptobenzimidazole compounds contain both -NH and -SH groups and alkylation was noticed to be more inclined to occur on sulphur rather than nitrogen due to higher nucleophilicity of sulphur in comparison with nitrogen [5]. Moreover; alkylation of 2-mercapto benzimidazole under basic conditions using different alkyl halides and aryl halides give the thioether derivatives [6].

On other hand, Triazoles are five-membered heterocyclic compounds which contain three nitrogen atoms [7]. Different synthetic methodologies have been utilized recently to prepare triazole ring system 1,3-dipolar cycloaddition reactions of azides with (alkyne [8], α,β-unsaturated ketones with azides [9] and from arylglyoxaldoxime) [10]. Many 1,2,3-triazoles are found to be potent anti-microbial [11], anti-inflammatory [12], antimalarial [13], antiviral agents [14] and a unit of high significance with anticancer profile in many of the human cell lines [15]. Pyrazoles are heterocyclic organic compounds characterized by a five-membered ring of 3 carbon atoms and two adjacent nitrogen centers [16]. Generally speaking, pyrazoles are synthesized by reaction of 1,3-diketones with hydrazine, 1,3-dipolar cycloaddition of diazo compounds with alkynes and reaction of α,β-unsaturated aldehydes and ketones with hydrazine [17]. Interestingly enough: a large number of pyrazoles have been produced and some of them gained applications on the clinical level as well. These compounds have diverse biological activities such as antimicrobial [18], anticancer [19], anti-inflammatory [20], antimicrobial and antioxidant [21].

In this research we aimed to synthesize new 2-chloro-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone derivatives including 1,2,3-triazole and pyrazole moieties and evaluation of its' antimicrobial activities.

MATERIALS AND METHODS

All chemicals used were supplied by: Merck, BDH, Fluka and Sigma Aldrich chemicals companies. The melting point was recorded using Gallenkamp, electro-thermal melting point apparatus. Infrared (IR) spectra were recorded using Fourier Transitions Infrared (FTIR-8400s) spectrometer Shimadzu, Japan, KBr disc in 4000-600 cm^{-1} spectral range, in the Department of Chemistry, College of Science, University of Baghdad and Research Laboratory, College of Pharmacy, University of Al-Mustansiriyah. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on NMR-Bruker, Ultra-shield 400 MHz, in the University of Ain-Shams, College of Pharmacy, Egypt. Also; Deuterated Dimethyl Sulfoxide (DMSO-d_6) was used as a solvent and Central Laboratory Isfahan University, Iran. Deuterated Chloroform ($CDCl_3$) was used as solvent.

Synthesis of 2-(methylthio)-1H-benzo[d]imidazole (1)

This compound was prepared according to the literature's procedure [6].

Synthesis of 2-chloro-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (2)

Solution of compound (1) (1 g, 0.006 mol) in anhydrous Dimethyl Formamide (DMF) (7 ml) was cooled to 0°C and sodium hydride (0.14 g, 0.006 mol) in small a portions was added. The solution was stirred for 30 min then chloroacetyl chloride (0.5 ml, 0.006 mol) was added drop wise. The mixture was stirred for 10 min at 0°C and then stirred at room temperature for (4 h). The solvent was evaporated then poured into ice water and filtered. The precipitate was recrystallized with ethanol to give a brown powder [22].

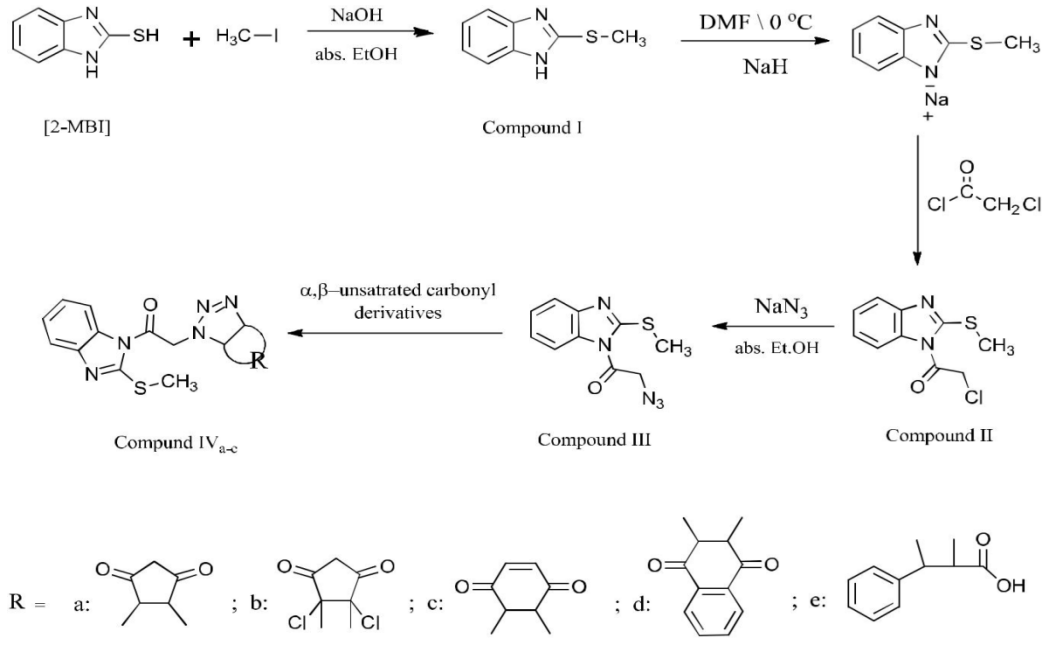
Synthesis of 2-azido-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (3)

Consequently, Sodium azide (0.52 g, 0.008 mol) was added to the solution of compound (2) (1 g, 0.004 mol) in absolute ethanol (10 ml). The mixture was refluxed for (6 h) with stirring. The solvent was evaporated then light brown precipitate was washed with cold water, filtrated and recrystallized with ethanol [23].

Synthesis of 2-(methylthio)-1H-benzo[d]imidazole triazole moiety derivatives (4a-e)

General procedure

Afterwards, α,β-unsaturated carbonyl compounds (0.001 mol) was added to the solution of compound (3) (0.25g, 0.001 mol) in absolute ethanol (10 ml). The mixture was refluxed for (24 h). The solvent was evaporated and the residue was washed with diethyl ether. As shown in Scheme 1 [24].



Scheme 1: Shows the synthesis of the target compounds (4a-e)

2-(methylthio)-1H-benzo[d]imidazole (1)

[$C_8H_8N_2S$]: 77% yield; m.p. 196-200°C; FTIR (cm^{-1}): 3120 (NH), 3053 (Ar-H), 2960 & 2872 (CH aliphatic), 1620 (C=N imidazole), 1500 & 1465 (C=C Aromatic), 665 (C-S); ^{1}H-NMR (δ ppm): 2.70 (S-CH_3), 7.09-7.43 (aromatic ring), 12.5 (NH).

2-chloro-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (2)

[$C_{10}H_{10}N_2SOCl$]: 85% yield; m.p. 120-126°C; FTIR (cm^{-1}): 3061 (Ar-H), 2955, 2924 & 2854 (CH aliphatic), 1718 (C=O amide), 1616 (C=N imidazole), 1570 & 1502 (C=C Aromatic), 794 (C-Cl); ^{1}H-NMR (δ ppm): 2.70 (S-CH_3); 4.28 (CH_2-Cl), 7.11-7.45 (aromatic ring), ^{13}C-NMR (δ ppm): 40.80 (S-CH_3), 70.27 (CH_2-Cl), 113-139 (aromatic ring), 156.10 (N=C-N), 173.60 (C=O amide).

2-azido-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (3)

[$C_{10}H_{10}N_5SO$]: 80% yield; m.p. 180-184°C; FTIR (cm^{-1}): 3053 (Ar-H), 2954, 2924 & 2808 (CH aliphatic), 2129, 1437 (N_3), 1710 (C=O), 1616 (C=N imidazole), 1589-1498 (C=C Aromatic).

1-(2-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)-2-oxoethyl)-1H-furo[3,4-d][1,2,3]triazole-4,6 (3aH,6aH)-dione (4a)

[$C_{14}H_{11}N_5O_4S$]: 70% yield; m.p. 98-100°C; FTIR (cm^{-1}): 3051 (Ar-H), 2950, 2922 & 2800 (CH aliphatic), 1850 & 1780 (C=O anhydride), 1710 (C=O amide), 1620 (C=N imidazole), 1550-1450 (C=C Aromatic), 1440 (N=N), 1270 (C-O-C).

3a,6a-dichloro-1-(2-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)-2-oxoethyl)-1H-furo[3,4-d] [1,2,3]triazole-4,6(3aH,6aH)-dione (4b)

[$C_{14}H_9N_5O_4SCl$]: 65% yield; m.p. 90-92°C; FTIR (cm^{-1}): 3063 (Ar-H), 2960, 2918 & 2841 (CH aliphatic), 1800 & 1726 (C=O anhydride), 1680 (C=O amide), 1620 (C=N imidazole), 1593 & 1525 (C=C Aromatic), 1446 (N=N), 1259 (C-O-C), 1018 (C-Cl); ^{1}H-NMR (δ ppm): 2.7 (S-CH_3), 3.39 (CH_2), 7.09-7.11 (aromatic ring); ^{13}C-NMR (δ ppm): 40.4 (S-CH_3), 78 (CH_2-Cl), 105.26 (C-Cl), 116.26-139 (aromatic ring), 150.1 (N=C-N), 174.0 (C=O amide), 188.6 (O=C-O).

1-(2-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)-2-oxoethyl)-1H-benzo[d][1,2,3]triazole-4,7-(3aH, 7aH)-dione (4_c)

[$C_{16}H_{13}N_5O_3S$]: 89% yield; m.p. 116-120°C; FTIR (cm^{-1}): 3055 (Ar-H), 2956, 2924 & 2854 (CH aliphatic), 1730 (C=O ketone), 1700 (C=O amide), 1612 (C=N imidazole), 1591-1508 (C=C Aromatic), 1437 (N=N).

1-(2-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)-2-oxoethyl)-1H-naphtho[2,3-d][1,2,3]triazole 4,9(3aH,9aH)-dione (4d)

[$C_{20}H_{15}N_5O_3S$]: 95% yield; m.p. 110-116°C; FTIR (cm^{-1}): 3057 (Ar-H), 2962, 2926 & 2862 (CH aliphatic), 1730 (C=O ketone), 1684 (C=O amide), 1589-1496 (C=C Aromatic), 1438 (N=N); ^{1}H-NMR (δ ppm): 2.7 (S-CH_3), 3.39 (CH_2), 5.7 (CH-quinone ring), 7.11-7.98 (aromatic ring); ^{13}C- NMR (δ ppm): 40.39 (S-CH_3), 78.2 (CH_2-Cl), 85.6 (CH-N), 121.69 (aromatic ring), 151.65 (N=C-N), 175.1 (C=O amide), 194.8 (C=O diketone).

1-(2-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)-2-oxoethyl)-5-phenyl-4,5-dihydro-1H-1,2,3 triazole-4-carboxylic acid (4e)

[$C_{19}H_{17}N_5O_3S$]: 90% yield; m.p. 120-124°C; FTIR (cm^{-1}): 3300-2700 (OH acid), 3053 (Ar-H), 2956, 2924 & 2854 (CH aliphatic), 1720 (C=O acid), 1687 (C=O amide), 1633 (C=N imidazole), 1550-1498 (C=C Aromatic), 1440 (N=N).

Synthesis of 2-((4-aminophenyl)amino)-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (5) [24]

Compound (2) (0.72 g, 0.003 mol) was dissolved in absolute ethanol (10 ml) then anhydrous potassium carbonate (0.41 g, 0.003 mol) was added. The mixture was stirred then *p*-phenylenediamine (0.32 g, 0.003 mol) solution in absolute ethanol (10 ml) was added drop-wise. The mixture was refluxed and stirred for (8 h). The solvent was evaporated and the product was washed with cold water, filtrated and recrystallized with (ethanol-water).

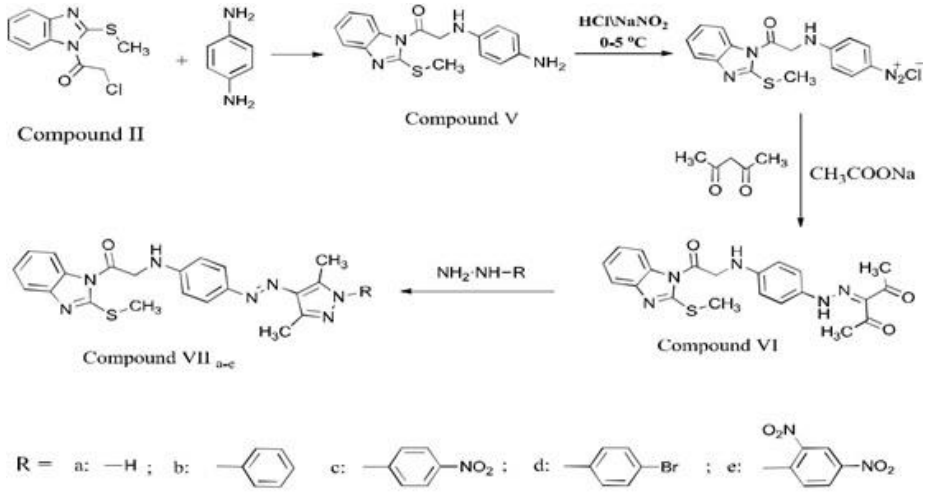
Synthesis of 3-(2-(4-((2-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)-2-oxoethyl) amino) phenyl) hydrazono) pentane-2,4-dione (6)

Compound (5) (0.31 g, 0.001 mol) was dissolved in concentrated HCl (2 ml) and cooled in an ice bath at 0-5°C, then drop-by-drop solution of Sodium nitrite (0.07 g, 0.001 mol) in (5 ml) water was added to it, stirred for (30 min) and the temperature was maintained at 0-5°C. The mixture was added drop-by-drop to acetyl acetone (0.1 g, 0.001 mol), sodium acetate (0.16 g, 0.002 mol) in absolute ethanol (5 ml) solution. The mixture was stirred for (30 min). Then after the solvent was left to evaporate, the product was recrystallized with ethanol [25].

Synthesis of 2-(methylthio)-1H-benzo[d]imidazole pyrazole moiety derivatives (7a-e)

General procedure

Hydrazine derivatives compounds (0.0006 mol) were added to compound (6) (0.25g, 0.0006 mol) in absolute ethanol (10 ml) solution. The mixture was stirred and refluxed for (10-12 h), the solvent was evaporated and the product was washed with water then diethyl ether. As shown in Scheme 2 [26].



Scheme 2: Shows the synthesis of the target compounds (7a-e)

2-((4-aminophenyl)amino)-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (5)

[$C_{16}H_{16}N_4SO$]: 68% yield; m.p. 102-110°C; FTIR (cm^{-1}): 3369 (asy.) & 3323 (sym.) (NH_2), 3215 (NH), 3059 (Ar-H), 2926 & 2816 (CH aliphatic), 1700 (C=O amide), 1618 (C=N imidazole) 1600 & 1552 (C=C Aromatic), 831 (p-NH_2); ^{1}H-NMR (δ ppm): 2.68 (S-CH_3), 3.35 (CH_2), 6.5 (NH_2), 7.09-7.11 (aromatic ring), 7.43 (NH); ^{13}C-NMR (δ ppm): 40.61 (S-CH_3), 65 (CH_2-Cl), 121.71 (aromatic ring), 151.65 (N=C-N), 174.3 (C=O amide).

3-(2-(4-((2-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)-2-oxoethyl)amino)phenyl)hydrazono) pentane-2,4-dione (6)

[$C_{21}H_{21}N_5SO_3$]: 93% yield; m.p. 78-83°C; FTIR (cm^{-1}): 3311 (NH), 3051 (Ar-H), 2958,2924 & 2858 (CH aliphatic), 1730 (C=O ketone), 1700 (C=O amide), 1624 (C=N imidazole & C=N of α,β-unsaturated carbonyl), 1589-1512 (C=C Aromatic); ^{1}H-NMR (δ ppm): 2.63 (S-CH_3), 2.76 (CH_3-C=O), 3.01 (CH_2), 5.9 (NH-N=C), 7.36-7.7 (aromatic ring), 7.8 (NH-CH_2).

(E)-2-((4-((3,5-dimethyl-1H-pyrazol-4-yl)diazenyl)phenyl)amino)-1-(2-(methylthio)-1H-benz [d]imidazol-1-yl)ethanone (7a)

[$C_{21}H_{21}N_7SO$]: 80% yield; m.p. 80-83°C; FTIR (cm^{-1}): 3325 (NH), 3049 (Ar-H), 2960,2945 & 2826 (CH aliphatic), 1700 (C=O amide), 1624 (C=N imidazole & C=N pyrazole ring), 1435 (N=N).

(E)-2-((4-((3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)diazenyl)phenyl)amino)-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (7b)

[$C_{27}H_{25}N_7SO$]: 69% yield; m.p. 70-72°C; FTIR (cm^{-1}): 3211 (NH), 3039 (Ar-H), 2955 & 2856 (CH aliphatic), 1705 (C=O amide), 1656 (C=N imidazole & C=N pyrazole ring), 1596 & 1558 (C=C Aromatic), 1435 (N=N).

(E)-2-((4-((3,5-dimethyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl)diazenyl)phenyl)amino)-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (7c)

[$C_{27}H_{24}N_8SO_3$]: 75% yield; m.p. 110-113°C; FTIR (cm^{-1}): 3193 (NH), 3099 (Ar-H), 2923 & 2854 (CH aliphatic), 1701 (C=O amide), 1624 (C=N imidazole & C=N pyrazole ring), 1596 (C=C Aromatic), 1458 (N=N), 1517 (asy.) & 1344 (sym.) (NO_2). ^{1}H-NMR (δ ppm): 2.01 (CH_3-C=C), 2.98 (S-CH_3), 4.27 (CH_2), 7.47-7.82 (aromatic ring), 8.4 (NH-CH_2).

(E)-2-((4-((1-(4-bromophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)diazenyl)phenyl)amino)-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (7d)

[$C_{27}H_{24}N_7SOBr$]: 85% yield; m.p. 160-162°C; FTIR (cm^{-1}): 3342 (NH), 3060 (Ar-H), 2962, 2925 & 2864 (CH aliphatic), 1690 (C=O amide), 1650 (C=N imidazole & C=N pyrazole ring), 1590 & 1556 (C=C Aromatic), 1438 (N=N), 594 (C-Br).^{1}H-NMR (δ ppm): 2.12 (CH_3-C=C), 2.83 (S-CH3), 3.88 (CH_2), 7.30-7.51 (aromatic ring), 8.3 (NH-CH_2).

(E)-2-((4-((1-(2,4-dinitrophenyl)-3,5-dimethyl-1H-pyrazol-4-yl)diazenyl)phenyl)amino)-1-(2-(methylthio)-1H-benzo[d]imidazol-1-yl)ethanone (7e)

[$C_{27}H_{23}N_9SO_5$]: 86% yield; m.p. 144-147°C; IR (λ_{max} cm^{-1}): 3325 (NH), 3097 (Ar-H), 2928 & 2852 (CH aliphatic), 1700 (C=O amide), 1641 (C=N pyrazole ring), 1616 (C=N imidazole), 1591 (C=C Aromatic), 1460 (N=N), 1514 (asy.) & 1330 (sym.) (NO_2).

Table 1: Antimicrobial activity of synthesized compounds

Sample code and standard	Concentration (µg/ml)	Zone of inhibition (mm)				
		Gram-positive		Gram-negative		Fungal
		Streptococcus faecalis	*Staphylococcus aureus*	*Escherichia coli*	*Klebsiella pneumonia*	*Candida albicans*
4a	800	-	12	2	-	2
	400	-	10	18	-	4
4b	800	-	14	18	-	6
	400	-	14	12	-	4
4c	800	-	10	8	-	4
	400	-	10	4	-	2
4d	800	-	12	4	-	4
	400	-	12	4	-	2
4e	800	6	12	4	-	4
	400	4	12	4	-	6
7a	800	4	20	6	-	8
	400	6	12	4	-	6
7b	800	4	12	6	-	4
	400	4	14	4	-	2
7c	800	4	12	4	-	-
	400	4	14	4	-	4
7d	800	2	12	12	-	18
	400	4	14	6	-	18
7e	800	4	12	6	-	6
	400	4	10	4	-	6
Ciprofloxacin	10	40	16	-	30	12
DMSO	-	-	-	-	-	-

Anti-microbial activity test

Some of the prepared compounds were tested clinically against two strains of bacteria Gram-positive bacterial isolates as: *Streptococcus faecalis* from the (ear) and *Staphylococcus aureus* from the (wound) and two strains from clinical Gram-negative bacterial isolates as: *Escherichia coli* from (urine) and *Klebsiella pneumonia* from the (ear) in addition to *Candida albicans* from (vagina) as fungus isolate.

The antimicrobial activities of each derivative compounds were studied by using agar well diffusion method, which used Mueller Hinton Agar (MHA) and Blood Agar Base (BAB). DMSO used as the negative controller and ciprofloxacin was used as a standard drug for antimicrobial. All tests were performed in college of Pharmacy/university of Al-Mustansiriyah. The results are displayed in Table 1 [27,28].

RESULTS AND DISCUSSION

Synthesis of the target compounds (4a-e and 7a-e) were detected by spectral (FTIR, ^{1}H-NMR and ^{13}C-NMR), sharped band in compound (2) in 1718 cm^{-1} that belongs to amide group because we have α-chloro to amide group that increased the frequency [29]. While, in (^{1}H-NMR) the chemical shift disappeared at 12.5 ppm that belongs to NH and in ^{13}C-NMR the signal appeared at 173 ppm for C=O amide. On other hand, the absorbed band in 1437-1446 cm^{-1} in compounds (4a-e) belongs to N=N group of triazole and disappeared at 2129 cm^{-1} for azide group in compound (3). In pyrazole compounds (7a-e) pathway synthesis, we have absorption band in compound (5) at 3369 (asym.) and (3323 sym.) for (NH_2) while in (^{1}H-NMR) we have signal at 6.5 ppm for (NH_2) and 7.43 ppm for (NH). In compound (VI) was disappeared (NH_2) band in (FTIR) and signal in (^{1}H-NMR).

The presence band in compound (7a-e) at 1435-1460 cm^{-1} which indicate the formation N=N and disappeared 1730 cm^{-1} that belonged to C=O of diketone in compound (6). Table 1 shows the inhibition zones in (mm) of the mentioned derivatives. In comparison with standard drug (Ciprofloxacin), the antimicrobial activity showed that compounds (4a-e and 7a-e) were specific for *E. coli* bacteria while showed no activity for *K. pneumonia* while in *S. faecalis* bacterial showed weak activity. Some of the prepared compounds showed high activity for *S. aureus* bacteria and *C. albicans* fungi.

CONCLUSION

This work demonstrates the reactions involved in the synthesis of new heterocyclic compounds and hence, the detection of their antimicrobial activity. The antimicrobial activity of these compounds was evaluated against Gram-positive, Gram-negative bacteria and fungi. The target compounds (4a-e and 7a-e) showed more significant antimicrobial activity than a standard well-known drug. On the other hand, most of the compounds showed a moderately significant antimicrobial activity.

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